SUMMARY MINUTES

MEETING OF THE

GENERAL AND PLASTIC SURGERY DEVICES PANEL

OPEN SESSION

MAY 5, 1997

9200 Corporate Boulevard
Rockville, MD

GENERAL AND PLASTIC SURGERY DEVICES PANEL MEETING

Attendees
May 5, 1997

Acting Chairperson
Monica Morrow, M.D.

Executive Secretary
Gail Gantt, R.N., M.G.A.

Voting Members
Titus Duncan, M.D.

Temporary Voting Members
Ricardo Azziz, M.D.
Narayan Deshmukh, M.B.B.S.
Thomas Downs, Ph.D.
Susan Galandiuk, M.D.
Barbara Levy, M.D.

Industry Representative
Cindy Domecus, R.A.C.

Consumer Representative
Sally Faith Dorfman, M.D.

FDA Representatives and Presenters
David B. Berkowitz, V.M.D., Ph.D.
Roxolana Horbowyj, M.D.
Stan Lin, Ph.D.
Stephen Rhodes, M.S.
Celia Witten, M.D., Ph.D.

OPENING REMARKS:

Executive Secretary Gail Gantt, R.N., opened the May 5, 1997 General and Plastic Surgery Devices Panel Meeting by reading the conflict of interest statement and the list of temporary voting members for this panel meeting. Ricardo Azziz, M.D., was granted a waiver for participation. Panel members then introduced themselves.

FDA representatives provided updates on the human tissue regulation initiative and previous panel recommendations. Celia Witten, M.D., Ph.D., described the regulatory framework for cells and tissues as a tiered approach based on risks to the patients. The framework was proposed by the Center for Biologics and addresses issues such as disease prevention, maintaining integrity in the regulatory process, assessment of safety and efficacy, and communications. According to Stephen Rhodes, M.S., FDA has approved the Premarket Application for Dermagraft-TC with the condition that the sponsor conduct post-approval market approval studies on 200 patients. FDA has received comments on the proposed reclassification of suction lipoplasty systems. Thus far comments have been supportive.

OPEN PUBLIC HEARING:

No comments were made.

OPEN COMMITTEE DISCUSSION:

Genzyme Corporation Presentation—PMA P960003:

The sponsor's representatives described the device (Sepracoat™); clinical problems caused by adhesions; clinical trial results, issues, and analyses; and use of the device in intra-abdominal surgery. The sponsor representative introduced the Sepracoat™ product as a device that is a 0.4% solution of sodium hyaluronate that reduces tissue damage and *de novo* adhesion development when applied during abdomino-pelvic surgery. After discussing the etiology and incidence of adhesions, the sponsor representative presented data on its multicenter, random, and placebo-controlled studies. According to principal investigators, Sepracoat™ reduced the incidence of available locations with *de novo* adhesions by 20% and the number of patients with at least one *de novo* adhesion by 7%. The safety profiles of the placebo and study groups were found to be nearly identical.

A sponsor representative addressed issues involving choice of endpoints, the study design and data analysis, treatment and investigator site interactions, the justification for statistical tests, and the integration of safety data. His analyses supported the sponsor's claims and were followed by a presentation on the device's utility in abdominopelvic surgery. A sponsor representative concluded that any adhesion can cause clinical problems and that no completely effective strategy exists for preventing *de novo* adhesions. The sponsor's summary concluded that Sepracoat™ has a favorable risk/benefit profile, and is safe, effective, and useful.

Panel Discussion:

In response to a question posed by the panel, the sponsor representative said that the issue of confining infections had not been looked into. Sponsor representative responses to further questions included the following: the majority of *de novo* adhesions (60-70%) result from laparotomies, 95% of the patients had indirect trauma, and 50% of the sites in trauma had adhesions not directly related to the trauma. Methods of standardization of adhesions across the different sites was discussed. The sponsor representative defined indirect trauma as damage to tissue that was not directly involved in the surgical procedure.

The sponsor's representatives responded to questions posed by Drs. Azziz and Morrow regarding choice of statistical tests, the masking/blinding of investigators, intra-observer variability, and the reproducibility of the scoring system. In their responses to these questions, the sponsor representatives indicated that the one-tail test is a more severe test than the two-tailed test, as it requires a higher level of evidence. The sponsor representatives went on to explain that neither the surgeon nor the blinded reviewer who was to review the video tapes of the surgeries knew which patients were given the placebo or the Sepracoat™ treatment. Finally, the sponsor representatives mentioned that there had been good correlation between the investigators and the blinded observers and that this was underlined by the good kappa correlation score, which was 0.7 between observers. Dr. Barbara Levy raised concerns about the four surgical sites that were identified as having statistically significant differences. She was also concerned with the second-look procedure with enterotomy, the use of anti-

inflammatory agents, and the packing of the bowel during the surgical procedure. Discussion ensued, concluding with an explanation of the application procedure. The sponsor's representatives stated that there were no significant allergic reactions, that analyses of variance were conducted one at a time except for demographic variables, and that there was no precipitation of antibiotics.

FDA Presentations:

FDA presenters summarized preclinical data and provided medical and statistical reviews. According to lead reviewer David Berkowitz, V.M.D., Ph.D., Sepracoat™ coating solution is indicated for reducing the incidence of newly formed adhesions resulting from incidental tissue damage. The solution is 0.4% hyaluronic acid in phosphate buffered saline (PBS) with a viscosity of 300-500 cP. He characterized the solution as a "normal constituent of extracellular space." He said that the effectiveness data were based on a rat cecal abrasion model, and the general toxicology studies using rabbits, guinea pigs, mice, and rats were negative. Dr. Berkowitz was not concerned with the findings from the baboon study that showed differences between the treatment and control groups. While concluding, he noted that the device does not affect antibiotic use, and it does not inhibit healing.

Medical reviewer Roxolana Horbowyj, M.D., provided a comprehensive review, describing the peritoneum, adhesion formation and incidence, device characteristics, and the study design and protocol. Results of three feasibility studies showed no serious device-

related or adverse events and acceptable handling characteristics.

The sponsor's pivotal study design characteristics included the following: two treatment groups (0.2% and 0.4% sodium hyaluronate) and a phosphate buffered saline (PBS) control group; 17 investigators at 23 investigational sites; and 362 patients. Results and the sponsor's claims were based on the cohort size of 107 patients (0.4% sodium hyaluronate) and 108 (PBS). Although the baseline demographic characteristics were similar between the control and treatment groups, the control patients had a greater number of pre-treatment lesions (4.5 $\pm$ 0.5 versus 3.2 $\pm$ 0.4). Between the groups, there was a statistically significant difference in adverse events. Although not device related, the sodium hyaluronate group suffered more unspecified pain, abdominal pain, nausea, dizziness, and pharyngitis. Twelve serious adverse events were also not device related.

Dr. Horbowyj concluded her presentation with a summary of effectiveness data and a set of questions for the panel to consider. The data show the incidence of patients with lesions was 95.4% for the PBS group and 88.8% for sodium hyaluronate group.

In his statistical review, Dr. Stan Lin summarized the sponsor's claims and then reanalyzed the claims of statistical significance of the efficacy data. He also addressed the adjustment of trial endpoints. Dr. Lin said that there are significant interaction effects; however, the trial was not designed to show interactive effects regarding treatment and site

differences. He added that the sponsor did not adequately address this issue. The difference between the two groups in terms of reducing *de novo* adhesions is not significant, he concluded.

Panel Reviews:

Titus Duncan, M.D., described the etiology, complications, morphogenesis, and devices used to prevent adhesions. He discussed issues from a general surgical perspective, and learned that no safety and efficacy data exist on the use of Sepracoat™ in patients following pelvic or abdominal irradiation. Dr. Titus concluded that the sponsor's study involved a "minuscule" number of patients. He said a prospective, randomized study would be needed to show clinical benefit (i.e., that the product reduces obstruction, pelvic pain, or infertility).

Barbara Levy, M.D., provided a gynecologist's perspective. She questioned if the number of adhesions was an adequate surrogate for fertility, obstruction, and pain; if all adhesions can be considered equal; and how a product designed for *de novo* lesions addresses the 30% general complication rate. Dr. Levy also questioned if more preexisting conditions and pathology can change the characteristics of the patients—for example, are they more prone to developing adhesions? Her concluding concern was the relevance of a gynecological model and study in respect to general surgical procedures. According to Dr. Levy, the data do not translate claimed benefits to clinical relevance.

Panel Discussion:

In response to the panelist' questions, the sponsor representatives explained the results of the baboon study (the increase in bleeding time) and clarified the administration procedure. Panel members then responded to questions posed by FDA, and Dr. Morrow stated the panel's consensus: (1) Regarding baseline patient characteristics, the panel remains concerned that the small difference in rate of efficacy may reflect biological diversity. (2a) The safety of 0.4% sodium hyaluronate is not a major clinical issue. (2b) There are no significant adverse risks posed by the use of this product. (3a) The level of reduction in *de novo* adhesions (88.8% versus 95.4%) is not clinically significant. Such a small difference cannot clearly demonstrate effectiveness. (3b) The mean proportion showing reduction in available sites is not clinically significant.

Panel members discussed the relevance of using a gynecological model, the use of a higher percentage of sodium hyaluronate, and the time it takes to administer the product. Dr. Lin restated his rationale for finding the sponsor's clinical results not statistically significant due to the variance in sites. The sponsor's representative responded, discussion was closed, and the panel was instructed on voting procedures.

Vote:

The panel voted unanimously that PMA P960003 is not approvable due to lack of evidence of clinical effectiveness. When polled for their reasons for voting affirmatively on

the motion to not approve the PMA, panel members said only a small difference was found between the two groups, which was not significant; and the evidence does not support the claim. To make the application approvable, Dr. Azziz said the sponsor should use a gynecological model, obtain follow-up data for at least 1 year, use the primary endpoint of incidence, and look at obstruction and pain. Patients should reflect a more homogeneous mix to avoid intra-site variance, according to Susan Galandiuk, M.D. Dr. Levy believes that the sponsor should use fewer sites and standardize the techniques (such as packing). Lastly, Narayan Deshmukh, M.D., recommends using temporary colostomy patients.

ADJOURNMENT:

The meeting was adjourned at 2:30 p.m.

I certify that I attended this meeting of the General and Plastic Surgery Devices Panel on May 5, 1997 and that these minutes accurately reflect what transpired.

Gail Gantt

Gail Gantt, RN
Executive Secretary, FDA

I approve the minutes of this meeting as recorded in this summary.

Monica Morrow

Monica Morrow, M.D.
Chairperson

Summary prepared by
Joëlle Lofton
for Elements in Style, Inc.
15065 Joshua Tree Road
North Potomac, MD 20878

Summary Edited by
David Krause on September 25 and October 16, 2000